Clinical eEvaluation of the safety Safety of adductiveAdductive-covered nitinol Nitinol stents Stents in the treatment Treatment of benign Benign tracheobronchial Tracheobronchial stenosisStenosis

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Short Titletitle: Clinical evaluation Evaluation of tracheobronchial Tracheobronchial stenosisStenosis

Synopsis: This This study is a Clinical evaluation of adductive-covered nitinol stents in the treatment of benign tracheobronchial stenosis. The viewpoint highlights adductive-covered nitinol stents can significantly reduce granulation tissue hyperplasia and are a good prospect for clinical application are a good prospect for clinical application in benign tracheobronchial stenosis treatment.

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ABSTRACT

Objective: To evaluate the effect of adductive-covered nitinol stents on tracheobronchial granulation tissue hyperplasia and assess the clinical application value.

Methods: Thirty-two patients were treated with ordinary-covered nitinol stents, and 28 patients were treated with adductive-covered nitinol stents. Bronchoscopy was performed in patients 2, 4, and 8 weeks after tracheobronchial stent implantation, and the occurrence and extent of granulation tissue hyperplasia were recorded simultaneously.

Results: Varying degrees of granulation tissue hyperplasia were observed in patients from both groups. The extent of granulation tissue hyperplasia in the group treated with adductive-covered nitinol stents was far less than the group treated with ordinary covered-nitinol stents.

Conclusion: Compared with ordinary-covered nitinol stents, adductive-covered nitinol stents can significantly reduce granulation tissue hyperplasia at both ends of the stent without any special side effects, and thus adductive-covered nitinol stents are a good prospect for clinical application in the treatment of benign tracheobronchial stenosis.

Keywords: stent; granulation tissue hyperplasia; tracheobronchial stenosis; interventional therapy

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Because of advantages, such as minimal invasiveness and rapid effect, nitinol stent implantation has a wide range of applications in the clinical treatment of tracheobronchial stenosis, but along with an increased number of treated cases and prolonged survival time of patients, some related complications, such as granulation tissue hyperplasia and associated tracheobronchial restenosis, have become a problem which plagues clinicians. Thus, follow-up treatment of stent-related granulation tissue hyperplasia imposes significant economic and psychological burden on the patients, and can limit the long-term efficacy of the stent (1, 2). Based on extensive clinical practice, we have modified the covered stents which are currently widely used in the clinic into covered nitinol stents which are adducted at both ends, and a good clinical effect has been achieved. The existing individual patient data were summarized and analyzed herein to determine the clinical application value of adductive-covered nitinol stents.

MATERIALS AND METHODS

Clinical data

There were a total of 60 patients with benign tracheobronchial stenosis, including 33 males and 27 females (age range, 18-63 years; mean age, 37 years). The patients with tracheobronchial stenosis caused by the invasion or oppression of malignant tumors were

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excluded. The patients were randomly divided into two groups using the coin toss method. Thirty-two patients were treated with ordinary-covered nitinol stents, and 28 patients were treated with adductive-covered nitinol stents. All patients had dyspnea pre-operatively, and were diagnosed with tracheobronchial stenosis by bronchoscopy. The average diameters of stenotic segments and adjacent normal trachea were obtained through CT examination of lungs on coronal and sagittal planes (average diameter = [transverse diameter + sagittal diameter] / 2), according to the percentage ratio of the diameter of the stenotic segment to the diameter of the normal segment. The extent of tracheobronchial stenosis was divided into four grades (3), as follows: grade I, ≤50%; grade II, 51%-70%; grade III, 71%-95%; and grade IV, 96%-99%. The general condition of the patients is shown in Table 1.

Treatment method

The patients in the ordinary stent group were treated with covered nitinol stents and a matched delivery system produced by Minimally Invasive Medical Technology Co., Ltd. (Nanjing, China). The patients in the adductive stent group were treated with adductive-covered nitinol stents, which were modified from ordinary stents according to our design requirement by Minimally Invasive Medical Technology Co., Ltd. The inner diameter of the stent was 10% larger than the normal trachea (the average value of the transverse and sagittal diameters), and the length of the stent was 20 mm longer than the stenotic segment (the two types of stents are shown in Figure 1). All patients in the bronchoscopy room received dicaine surface anesthesia and lidocaine cricothyroid membrane puncture anesthesia before surgery. The patients who could not cooperate were given anesthesia combined with

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intravenous propofol anesthesia by the anesthetist. The bronchoscope (Olympus 160;) was inserted through one nares into the trachea. The guide wire was inserted through the biopsy hole and the bronchoscope was withdrawn after the guide wire was passed through the stenotic segment of the trachea. The bronchoscope was inserted again through another nares and the assistant slowly sent the placement machine along the guide wire to pass through the stenotic segment and deliver the stent under bronchoscopic guidance. The bronchoscopy was performed in patients 2, 4, and 8 weeks post-operatively. The extent of granulomatous hyperplasia was recorded. The height of the granulation tissue extruding out of the mucosal surface was compared with the inner diameter of the corresponding stent, as follows: grade 1, the longest diameter of the granulation tissue was < 50% of the inner diameter of the stent; grade 2, the longest diameter of the granulation tissue was > 50% and < 70% of the inner diameter of the stent; grade 3, the longest diameter of the granulation tissue was > 70% and < 95% of the inner diameter of the stent; and grade 4, the longest diameter of the granulation tissue was > 95% and < 99% of the inner diameter of the stent.

All data were analyzed by SPSS 13.0 software. The measurement data are expressed as the mean ± standard deviation. The granulation tissue hyperplasia after stent implantation was compared between the two groups by the Ridit test. A P value <0.05 was considered statistically significant.

RESULTS

All patients underwent successful stent implantation one time, and the symptoms of dyspnea were significantly alleviated in all patients after stent implantation. The granulation tissue

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hyperplasia at both ends of the stent were observed 1 week after implantation of the covered stent, but most conditions were mild, did not affect ventilation, and thus needed no special treatment. Along with the prolonged implantation time, the granulation tissue hyperplasia was apparent. The extent of granulation tissue hyperplasia in the adductive stent group was significantly less than the ordinary stent group. One and 4 patients in the ordinary stent group had dyspnea 4 and 8 weeks after stent implantation, respectively. Bronchoscopy showed severe granulation tissue hyperplasia. The granulation tissue hyperplasia blocked the lumen in most cases. A high-frequency electric knife and cryotherapy to alleviate the dyspnea caused by granulation tissue hyperplasia was required in most cases. Although most patients in the adductive stent group also had granulation tissue hyperplasia, the extent was milder, the progress was slow, and none of the patients had dyspnea. Within the observation time limit, no other complications, such as stent displacement, stent fracture, sputum bolt formation, and tracheobronchial walls appeared in the two groups. The results of bronchoscopy in the two groups of patients after stent implantation and statistical analysis are shown in Table 2-4.

DISCUSSION

Common causes of benign tracheobronchial stenosis in clinics include orotracheal intubation or intubation after tracheotomy, endobronchial tuberculosis, post-operative trauma, Wegener's granulomatosis, and relapsing polychondritis. Endotracheal intubation and endobronchial tuberculosis are most commonly seen, and were also the main etiologies underlying tracheobronchial stenosis in the current study. With the continuous development of

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interventional techniques, the treatment of tracheobronchial stenosis eliminates disadvantages, such as major trauma and slow healing, and offers minimally invasive treatment within the trachea, which mainly includes stent implantation and balloon expansion. With respect to malignant tracheobronchial stenosis, the interventional treatment of benign tracheobronchial stenosis is more difficult. Due to the long survival of patients, in addition to the need to relieve the clinical symptoms of tracheobronchial stenosis, we should be concerned about the long-term prognosis of patients and avoid long-term complications caused by the treatments as much as possible (4, 5). It is crucial to reduce tissue irritation to reduce the granulation tissue hyperplasia caused by the treatment as much as possible.

Numerous studies indicate that the material, inner diameter size and implantation time of the stent and the physical condition of the patient has significant effects on the extent of granulation tissue hyperplasia in tracheobronchial mucosa after stent implantation (6-8). Although international scholars have suggested that the stents initially selected for benign lesions should be silicone stents, there are no such products available on the domestic market, therefore the metallic stent is still the first choice for relevant treatments in domestic hospitals.

Due to its good biocompatibility, safety, wear resistance, superelasticity, corrosion resistance, and unique shape memory effect, the nitinol memory stent is more widely recognized for use in domestic hospitals. Through extensive clinical experience, we found that granulation tissue hyperplasia after implantation of covered nitinol memory stents occurs mainly at both ends of the stent, which is consistent with the research results at home and abroad (7,9). Both ends are the locations where the supporting force is weakest, and the

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sticking between the stent and the tracheobronchial wall is also the poorest, which can lead to increased friction between the stent and the tracheobronchial wall. The repeated mechanical stimulation caused by metal material and friction can lead to tissue damage and inflammation. The granuloma will occur during the inflammatory repair process. If the mechanical stimulation cannot be eliminated in the short term, the granulation tissue will be gradually increased until restenosis occurs. According to this principle, we made changes to both ends of the stent, which were adducted. The ends of the stent showed arc-shaped transitions to the trunk, and stuck better to the trachea, which reduced the unequal stress surfaces at both ends of the stent and reduced the friction force between the stent and the mucosa. The results of this study showed that in the case of equal efficacy, the incidence and severity of granulation tissue hyperplasia at both ends of the adductive stent are lower than both ends of the ordinary stent. There were no differences in the occurrence rates of other complications, such as stent displacement and stent fracture,

At present, scholars at home and internationally have debated the use of metallic stents to treat tracheobronchial stenosis. A number of scholars have suggested discontinuing the implantation of metallic stents in patients with tracheobronchial stenosis (10, 11) because all types of metallic stents stimulate granulation tissue hyperplasia. Severe granulation tissue hyperplasia can easily lead to severe tracheobronchial restenosis, so that the treatment of benign tracheobronchial restenosis has become more complex and the prognosis is poor. In addition, no other serious complications, such as stent fracture, tracheoesophageal fistulas, and sputum bolt obstruction were observed in patients of both groups in this study. It is considered that this may be related to improvement of the stent

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material and technology and the shorter implantation time of the stent. Related studies have shown that the shaping effect of metallic stents is generally completed within 3-6 months, and domestic scholars have suggested that the appropriate implantation time of covered stents for treatment of benign tracheobronchial restenosis is about 3.5 months, which means that within a period of time when the stent plays a role, the incidence of granulation tissue can be significantly reduced. The metallic stent implantation can be carried out more widely in the clinic so that more patients with tracheobronchial restenosis can benefit.

CONCLUSION

The adductive stent can be made by making minor changes according to physical principles on the basis of ordinary covered stents. The adductive stent is easy to operate, creates no additional economic burden on patients, and reduces the incidence of granulation tissue hyperplasia after implantation. The adductive stent is a method which is worth popularizing in the clinic and has good application prospects.

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~~Author Contributions~~AUTHORS' NOTE

Beibei Sun performed the statistical analysis, Fan Cao conceived of the study, Yong Qi and

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Yun Ma participated in its design,Lijun Ma wrote this paper ,Xianliang Chen read and approved this study.The authors declare that they have no conflicts of interest.

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.	Adductive stent	Ordinary stent
Number of cases	28	32
Number of stents	28	32
Age	38±13	36±10
Gender (male/female)	15/13	18/14
Pathogenesis		
Non-specific inflammation	1	2
After endotracheal intubation	18	20
Benign tumor	3	5
After tracheobronchial operation	6	5
Stenotic location		

Table 1: Relevant data of patients in the two groups

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Upper segment of the trachea		7	7
Middle segment of the trachea		9	14
Lower segment of the trachea		12	11
Stenotic length （mm）		25.8±3.9	27.5±3.8
Stenotic extent （Grades）	Grade I	0	0
	Grade II	8	12
	Grade III	18	19
	Grade IV	2	1

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Table 2. Status of granulation tissue hyperplasia 2 week after implantation of the

Group	Status of granulation tissue hyperplasia				
	No granulation tissue hyperplasia	Grade 1	Grade 2	Grade 3	Grade 4
Ordinary stent	20	7	5	0	0
Adductive stent	21	5	2	0	0
Total	41	12	7	0	0
U value	1.114				
P value	0.031				

Table 3: Status of granulation tissue hyperplasia 4 week after implantation of the two types of stents

Group	Status of granulation tissue hyperplasia				
	No granulation tissue hyperplasia	Grade 1	Grade 2	Grade 3	Grade 4
Ordinary stent	18	5	8	1	0
Adductive stent	19	5	4	0	0
Total	37	10	12	1	0
U value	1.283				

P value	0.041

Group	Status of granulation tissue hyperplasia				
	No granulation tissue hyperplasia	Grade 1	Grade 2	Grade 3	Grade 4
Ordinary stent	10	10	8	4	0
Adductive stent	11	11	6	0	0
Total	21	21	14	4	0
U value	1.342				
P value	0.043				

~~**Figure Legends**~~

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~~Fig.1. The exterior shapes of the two types of stents.~~

Figure: The exterior shapes of the two types of stents.

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